TITLE OF THE INVENTION

COMPOSITE MATERIAL AND PROCESS FOR INCREASING BIOAVAILABILITY AND ACTIVITY OF A BENEFICIAL AGENT

BACKGROUND OF THE INVENTION

1. Field of the Invention

This application is a Continuation-in-Part of U.S. Application Ser. No. 09/641,120, filed on August 17, 2000. The present invention relates in general to a composite material, and more particularly, to a composite material having a beneficial agent associated with another component having a greater hardness than the beneficial agent. Such a composite material enables increased bioavailability and/or activity of the beneficial agent, and can be used in numerous applications, including topical, oral and/or systemic administration of a medicament, pharmaceutical agent, chemical agent, etc.

2. Background Art

Beneficial agents have been known in the art for years and are the subject of numerous patents, including U.S. Pat. No. 4,344,934, U.S. Pat. No. 4,517,179, and U.S. Pat. No. 5,641,515.

U.S. Pat. No. 4,344,934 discloses medical compositions comprising wetted mixtures of poorly soluble drugs with water soluble polymers which are useful in increasing bioavailability of associated drugs.

U.S. Pat. No. 4,517,179 discloses rapidly dissolving uniform compositions of low water solubility drugs formed from a dry mixture of the drug having a reduced particle size in combination with properly selected and sized excipients including microcrystalline cellulose, dibasic calcium phosphate, starches and a lubricant.

U.S. Pat. No. 5,641,515 discloses a controlled release pharmaceutical formulation comprising nanoparticles formed of a biodegradable polycyanoacrylate polymer in which insulin is entrapped.

While beneficial agents have become common in numerous applications, the efficiency of their administration remains problematic for several applications. In particular, numerous beneficial agents comprise molecules that are undesirably insoluble in an associated environment to the extent that they are not sufficiently bioavailable during a predetermined administration period. One way to increase the solubility of the beneficial agent is by configuring the beneficial agent into nanoparticles. However, in doing so these agents commonly aggregate, conglomerate, and/or coagulate. Upon aggregation, conglomeration, and/or coagulation, the effective surface area of the beneficial agent can be dramatically decreased. As a result, the beneficial agent is not effectively soluble, and, in turn, truly bioavailable, due to decreased surface area of the beneficial agent.

It is therefore an object of the present invention to increase the bioavailability of a beneficial agent associated with a component by ensuring that the component has a greater hardness than the beneficial agent. When the relative hardnesses of each of the two materials is maintained, the bioavailability and activity of the beneficial agent can be improved substantially.

Further, it is also an object of this invention to provide a component that, by its very chemical makeup, aids in increasing the bioavailability of a beneficial agent.

These and other objects of the present invention will become apparent in light of the present specification, claims, and drawings.

SUMMARY OF THE INVENTION

The present invention is directed to a composite material suitable for external and/or internal association with a living body comprising: (1) a component having a surface area; and (2) a first beneficial agent applied to at least a portion of the surface of the component; wherein (3) the component is fabricated from a material having a hardness greater than the hardness of the first beneficial agent to, in turn, increase bioavailability of the first beneficial agent.

Preferably, the component comprises: (1) a diameter of less than 4 microns, but preferably less than 1 micron; and (2) a substantially inert material. It is also contemplated that the inert component be fabricated from either a hygroscopic or hydrated material.

It is preferable to manufacture the component from a material that is either (1) effervescent, or (2) inert and soluble in a biochemical environment. For example, the component could be manufactured from a carbonaceous material such as a metal carbonate or metal bicarbonate.

In another preferred embodiment of the invention, the component is fabricated from at least one material selected from the group consisting essentially of noble metals such as Ag, Pt, Rh, Au, etc., metal oxides, metal nitrides, metal carbides, metal phosphates, carbonaceous materials, bicarbonate material, phosphates, ceramic materials, and mixtures thereof.

In yet another preferred embodiment of the invention, the component is fabricated from at least one material selected from the group consisting essentially of zeolites,

Ag_2O, Ag, Au, Ta_2O_5, Al_2O_3, TiO_2, C, SiO_2, Bi_2O_3, ZnO and mixtures and compounds thereof. In such an embodiment, the component may be fabricated from an antibacterial material. In an alternative embodiment of the present invention, the component could be fabricated from hydrated ceramic materials.

In accordance with the present invention, the first beneficial agent is fabricated from at least one material selected from the group consisting essentially of a pharmaceutical agent, a medicament, a chemical agent, and mixtures thereof. The first beneficial agent may also be associated with an effervescent material.

Additionally, a second beneficial agent may be processed such that the composite is formed between the second beneficial agent and the first beneficial agent. In this embodiment, the first beneficial agent may be fabricated from a material having a hardness and surface area greater than the hardness and surface area of the second beneficial agent.

The present invention is also directed to a composite material suitable for external and/or internal association with a living body comprising: (1) a first beneficial agent; and (2) a second beneficial agent associated with at least a portion of the surface of the first beneficial agent, wherein the first beneficial agent is fabricated from a material having a hardness greater than the hardness of the second beneficial agent to, in turn, increase bioavailability of the second beneficial agent relative to the first beneficial agent.

Preferably, the first beneficial agent comprises a core particle, wherein the core particle has a diameter of less than 4 microns, and even more preferably less than 1

micron. It is also preferred that the first beneficial agent have a surface area of less than 10 m^2/g, and even more preferably less than 0.5 m^2/g.

In a preferred embodiment of the invention, a tertiary beneficial agent may also be associated with at least a portion of the surface of the second beneficial agent.

The present invention is additionally directed to an alternative composite material suitable for external and/or internal association with a living body comprising: (1) a component having a surface area; (2) a first beneficial agent applied to at least a portion of the surface of the component; wherein (3) the component is fabricated from a material having a hardness greater than the hardness of the first beneficial agent; and wherein (4) the component serves to increase the effective surface area of the beneficial agent relative to a beneficial agent unassociated with a component, and, in turn, to increase bioavailability of the first beneficial agent. The component preferably has a surface area of less than 10 m^2/g, and a diameter of less than 4 microns.

The present invention is also directed to a process for fabricating a composite material comprising the steps of: (1) providing a component having a hardness; (2) providing a first beneficial agent having a hardness less than the hardness of the component to, in turn, increase bioavailability of the first beneficial agent; and (3) associating the first beneficial agent with at least a portion of the surface of the component. The component preferably has a surface area of less than 10 m^2/g, and a diameter of less than 4 microns.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described with reference to the drawings wherein:

Figs. 1a and 1b of the drawings are schematic representations of a first embodiment of a composite material fabricated in accordance with the present invention;

Figs. 2a and 2b of the drawings are schematic representations of a second embodiment of a composite material fabricated in accordance with the present invention;

Figs. 3a, 3b and 3c of the drawings are schematic representations of a third embodiment of a composite material fabricated in accordance with the present invention;

Figs. 4a, 4b and 4c of the drawings are schematic representations of a fourth embodiment of a composite material fabricated in accordance with the present invention; and

Fig. 5 of the drawings is a schematic representation of a fifth embodiment of a composite material fabricated in accordance with the present invention.

DETAILED DESCRIPTION OF THE INVENTION

While this invention is susceptible of embodiment in many different forms, there is shown in the drawings and described herein in detail several specific embodiments with the understanding that the present disclosure is to be considered as an exemplification of the principles of the invention and is not intended to limit the invention to the embodiments illustrated.

It will be understood that like or analogous elements and/or components, referred to herein, are identified throughout the drawings by like reference characters.

Referring now to the drawings and to Fig. 1a and 1b in particular, composite material 10 is shown in a first embodiment as generally comprising component 12 having a surface 14, and first beneficial agent 16 associated with at least a portion of surface 14 of the component 12. Component 12 may additionally be labeled as particle 12, or core particle 12. However, for the sake of convenience and consistency, component 12 will be referred to component 12 throughout the specification and claims. As will be discussed in greater detail below, component 12 and first beneficial agent 16 of composite material 10 are fabricated from materials suitable for external and/or internal association with a living body, such as a human, cow, horse, dog, bird, fish, etc. As such, it is desirous to utilize materials for composite material 10 that maximizes its administration efficiency and minimizes administration cost and/or toxicity.

Component 12 is preferably fabricated from a material having a hardness greater than the hardness of first beneficial agent 16. It will be understood that when the hardness of component 12 is greater than the hardness of first beneficial agent 16, the

first beneficial agent will, upon association with surface 14 of component 12, substantially increase its bioavailability and/or activity.

The effective surface area of component 12 may vary depending upon the conditions of intended use, and has been capable of providing adequate bioavailability over a wide range of surface areas. Effective bioavailabilities have been found, in the past, for components 12 having a surface area of greater than 10 m^2/g. However, in the present invention it will be understood that a preferred effective surface area of less than approximately 10 m^2/g is desirous, although the teachings of the present invention may be applied to any number of surface areas, including those above 10 m^2/g. Even more preferably, the effective surface area of component 12 can be less than 0.5 m^2/g. Component 12 may vary in diameter to any diameter less than 400 nanometers (4 microns), and more preferably from less than 1 to approximately 100 nanometers.

As previously discussed, component 12 is fabricated from a material suitable for internal and/or external association with a living body. As such, component 12, is preferably, substantially inert with respect to a living body. Examples of suitable materials include, noble metals (e.g. Ag, Pt, Rh, Au, etc.), metal oxides (e.g. Ag_2O, Ag, Au, Ta_2O_5, Al_2O_3, TiO_2, Bi_2O_3, ZnO, $CaCO_3$, MgPO4 etc.), metal nitrides, metal carbides, carbonaceous materials, bicarbonate materials such as sodium bicarbonate, phosphates ceramic materials, zeolites and mixtures thereof are especially useful in applications where it is desirous for the component to exhibit antibacterial properties.

Where the component particle is fabricated from metal carbonates or metal bicarbonates, an interesting effect is achieved. Specifically, the combination of a component particle made of such materials, and a beneficial agent (described below), creates a particle that generates a gas upon contact with bodily fluids. Inorganic compounds such as metal carbonates react with bodily fluids to split the carbonate portion of the particle into gaseous elements such as oxygen or carbon dioxide. Essentially, therefore, when the component particle is manufactured with at least a portion having metal carbonates or metal bicarbonates therein, the component acts as an evervescent base to aid in increasing bioavailability of the associated beneficial agent. Other, similar materials could also be used to achieve this effervescent effect from the component particle itself.

In a related embodiment, the component particle could be manufactured from a bio-soluble material to also increase the bioavailability of the associated beneficial agent. A bio-soluble material is one that dissolves upon exposure to a biochemical environment or bodily fluid. A component particle that is at least partially composed of a bio-soluble material will begin to dissolve upon exposure to an appropriate environment, whereafter the exposed surface area of the associated beneficial agent is increased. The increase in the exposed surface area, in turn, increases the bioavailability of the beneficial agent.

First beneficial agent 16 is fabricated from a material that is capable of performing a material benefit to a living body. Examples of such materials include, a pharmaceutical agent, a medicament, a chemical agent, and mixtures thereof.

As is best shown in Figs. 2a and 2b, composite material 10 may also include second beneficial agent 18, which can be applied to at least a portion of surface 20 of first beneficial agent 16. In this embodiment, it is desirous for first beneficial agent 16 to be fabricated from a material having a hardness greater than the hardness of second beneficial agent 18. It will be understood that when composite material 10 comprises multiple beneficial agents, the beneficial agents may function independently of each other, or alternatively, may function together to, for example, generate a derivative species within/with on the living body.

In a third embodiment of the present invention, and as is best shown in Figs. 3a, 3b and 3c, first beneficial agent 16 can be associated with effervescent material 17. Effervescent material 17 serves to further increase the bioavailability and/or activity of first beneficial agent 16 upon placement in, for example, an aqueous medium. It will be understood that the composition and availability of numerous effervescent materials is well known in the art.

Referring now to Figs. 4a, 4b and 4c, composite material 10 is shown as comprising first beneficial agent 16 having surface 20, and second beneficial agent 18 associated with at least a portion of surface 20 of first beneficial agent 16. Similar to the above-provided embodiments, it is desirous for first beneficial agent 16 to be fabricated from a material having a hardness greater than the hardness of second beneficial agent 18. Although not shown, it is also contemplated that one or both of first and second beneficial agents 16 and 18, respectively, can be associated with an effervescent material 21.

As is shown in Fig. 5, tertiary beneficial agent 22 can be associated with at least a portion of surface 24 of second beneficial agent 18.

The present invention is also directed to a process for fabricating a composite material as disclosed herein. In first and second steps of the process, a component having a surface area and a beneficial agent are provided. The component preferably has a surface area of less than 10 m^2/gm. Once provided, the beneficial agent is associated with at least a portion of the surface area of the component. Such association may be occur via any one of a number of conventional methods, including, spraying, brushing, rolling, dip coating, powder coating, misting, and/or chemical vapor depositing the beneficial agent to at least a portion of the high surface area of the component. Although not necessary, the primary beneficial agent and/or the component can be milled to a predetermined dimension prior to or after association with each other.

As described above, in one embodiment the component material used in the above process preferably comprises an effervescent material. For example, the component could be manufactured from a metal carbonate or a metal bicarbonate material. In another embodiment, the component used in the process comprises an inert and bio-soluble material capable of dissolution upon introduction into an appropriate environment.

An alterative composite material can be fabricated in accordance with the present invention upon providing a first beneficial agent having a surface area of, for example, less than 10 m^2/gm, and a second beneficial agent. After the above-identified materials

have been provided, the second beneficial agent can be associated with at least a portion of the surface area of the first beneficial agent.

It will be understood that composite materials in accordance with the present invention can be administered externally or internally to a living body for numerous applications, wherein one or more beneficial agents maintain a predetermined effective surface area as a result of being associated with the surface of a small particle having a hardness greater than the hardness of the beneficial agent(s).

The efficacy of the current configuration was examined through a number of experiments (as will be described below). In these experiments, the dissolution (bioavailability) of bioactive components DHEA (first beneficial agent) and Cromax (another beneficial agent) in 0.9 % NaCl solution was compared between a composite of a low surface area inorganic compound (component) (Al_2O_3 with a surface area of 0.81 m^2/g) coated with DHEA and then Cromax, and virgin DHEA and Cromax powders. The coated inorganic composites and virgin beneficial agent species were inserted separately into NaCl solutions, and the dissolution of the species from the composites was compared against the dissolution of the species without a bioavailability composite.

Initially, two experiments were undertaken as controls, to establish the dissolution of both the individual DHEA and Cromax species in the 9% NaCl solution, without the aid of the bioavailability compound (harder component) or configuration.

a) EXPERIMENT 1: DHEA in 0.9% NaCl

In Experiment 1, approximately 13.45 grams of 0.9% NaCl was added to 0.05 grams of DHEA in a test tube. The test tube was shaken and allowed to sit for 20 minutes, while shaking periodically. It was observed that the DHEA compound did not release readily into the NaCl solution, but instead coagulated into clumps upon contact with the NaCl solution.

b) EXPERIMENT 2: Cromax in 0.9% NaCl

In Experiment 2, approximately 13.0 g of 0.9% NaCl was added to 0.05 g of Cromax in a test tube. The test tube was shaken and allowed to sit for 20 minutes with periodic shaking. When the 0.9% NaCl was first poured in the test tube it became slightly red, while chunks of particles remained suspended in the solution itself. From observation, it appeared that the Cromax did not readily release into the NaCl solution.

As can be seen, pure DHEA and Cromax species had difficulty dissolving directly into the 9% NaCl solution. The failure of these species to dissolve adequately in the solution shows the significant need for something to aid dissolution.

In anticipation of the latter part of the experiments, the respective DHEA and Cromax compounds in Al_2O_3 were prepared by dispersing the Al_2O_3 (A14 Grade) in ethyl alcohol with tween 80 dispersant. The Al_2O_3 species provides the component (core particle) part of the present invention, having a hardness greater than both the DHEA and the Cromax species. As will be described in the experiments below, it was observed that once those species are applied to the Al_2O_3, the difference in hardnesses between the

component (Al_2O_3) and the deposited beneficial material (either DHEA or Cromax) allows the beneficial material to be exposed to and dissolved into the surrounding solution with greater ease than introducing the beneficial materials alone.

In assembling the composite species, the DHEA and Cromax at 50-wt % each with respect to Al_2O_3 were added to individual nalgene bottles with pre-dispersed Al_2O_3 (having approximately 0.81 m^2/g surface area) and allowed to mix on a paint shaker for 30 minutes. The mixed compounds were allowed to dry at 37°C to evolve ethyl alcohol, and the drug compounds precipitated uniformly on the Al_2O_3 particles. The dry powder blends were screened through -325-mesh with a 40-micron opening to break up the soft agglomerates. Thereafter, various makeups of the composite materials were tested for their ability to allow the DHEA and/or Cromax to dissolve in the NaCl solution.

c) EXPERIMENT 3: 50 wt % DHEA/50 wt % Al_2O_3 in 0.9% NaCl

In Experiment 3, approximately 13.45 grams of 0.9% NaCl was added to 0.113 grams of 50-wt % DHEA/50 wt % Al_2O_3 in a test tube. The test tube was shaken and allowed to sit for 20 minutes with periodic shaking. The DHEA/ Al_2O_3 compound was immediately released into the NaCl solution, forming a cloudy solution. The release of DHEA was observed to be immediate and controlled.

d) EXPERIMENT 4: 50 wt% Cromax/50 wt% Al_2O_3 in 0.9% NaCl

In Experiment 4, approximately 13.45 grams of 0.9% NaCl was added to 0.103 grams of 50 Cromax in a test tube. The test tube was shaken and allowed to sit for 20 minutes with periodic shaking. When the 0.9% NaCl was poured into the test tube, the manufactured compound immediately released into the NaCl solution and became cloudy right away. The release of Cromax appeared to be controlled and immediate.

As can be seen, the compound species having precipitated DHEA and Cromax thereon significantly increased the dissolution/bioavailability of those species in the 0.9% NaCl solution. Contrarily, when virgin DHEA and Cromax were introduced into the same 0.9% NaCl solution, the compounds tended to coagulate and form clumps. It is clear from the experiments that the presence of a component as the core portion of a composite particle can increase the dissolution and thus bioavailability of species deposited on that particle. In the present experiment, the core particle used, Al_2O_3, has a greater hardness than both of the species that were deposited on it, including DHEA and Cromax. Therefore, it was observed that the presence of a component having a greater hardness than the deposited material helps to increase the bioavailability of the deposited substances.

Additionally, the increased bioavailability observed in the present invention did not appear to be affected by the relatively low surface area of the inorganic compound (namely the Al_2O_3 with a surface area of 0.81 m^2/g). Thus, smaller component particles can be used with the present invention to increase bioavailability, without sacrificing the efficacy of the device.

The foregoing description merely explains and illustrates the invention and the invention is not limited thereto except insofar as the appended claims are so limited, as those skilled in the art who have the disclosure before them will be able to make modifications without departing the scope of the invention.